New Claims 59 and 60 are added to address the Examiner's concerns expressed on p. 6 of the Office Action (p.6, *ll.*14-16). Specifically, the newly added claims specify that the non-yeast or heterologous receptors (Claim 50 and 60, respectively) are not hybrid receptor proteins, however their genes may contain sequence elements, including yeast promoters and/or signal sequences, that enhance expression of a functional mature receptor in yeast. As the Examiner has noted, such claims are fully enabled by the instant application (see Office Action, p.6, *ll.*14-16).

I. REQUEST FOR INTERFERENCE UNDER 37 C.F.R. § 1.607 WITH U.S. PATENT NO. 5,691,188 BY PAUSCH

Under separate cover, Applicants will submit a Request for Interference under 37 C.F.R. § 1.607 with U.S. Patent No. 5,691,188 by Pausch *et al.* (the "Pausch '188 patent"), which issued from Application Serial No. 08/195,729, filed on February 14, 1994. Attorneys for Applicants allege under 37 C.F.R. § 1.608(a) that there is basis upon which the applicant is entitled to judgment relative to the Pausch '188 patent. The reasons that form the basis for this allegation are set forth below.

II. WRITTEN DESCRIPTION SUPPORT IS FOUND FOR THE PENDING CLAIMS IN THE PARENT APPLICATION FILED MARCH 31, 1993

The original and newly added claims are fully supported by the written description of the specification and claims of the originally filed parent application, Application Serial No. 08/041,431, filed March 31, 1993 (the "parent '431" application). In particular, written description support for heterologous and non-yeast G protein-coupled receptors ("GPCRs") is found in the specification and claims of the parent application at p.14 *l.*23- p.16 *l.*26, and in the original claims on pp. 51-53. For example, clear written description support for genes encoding specific heterologous (*i.e.*, human) GPCRs listed in Table 1 operably linked to a promoter and a signal sequence functional in yeast is provided in the specification at p. 15, *ll.* 12-15. Specific support for non-yeast GPCRs is found in original claims 17-23, wherein the recited cells comprise non-yeast receptors.

An extensive list of heterologous and non-yeast GPCRs are enumerated in Table 1, which also provides reference citations for the sequences and expression constructs (see Table 1 and references cited therein, p. 39-49). A yeast cell comprising such a heterologous GPCR and hybrid Gα protein was constructed and is provided as Example 10 of the specification of the pending application (page 115, line 28, to page 120, line 14). This example of yeast cell comprising a gene encoding the human C5A receptor, a non-yeast and heterologous GPCR, finds support in the written description of the parent '431 application (see Table 1, p. 39, row 8 and p. 15, *ll.* 12-15, which provides all the sequences and methods used in the construction of these yeast cells). Numerous other heterologous receptors that function in yeast cells with hybrid Gα proteins are also described in the '431 application (*e.g.*, the f-Met-Leu-Phe receptor, see p. 40, row 7; ¶ 8 of the Broach Declaration filed January 3, 2003).

As such, the instantly claimed invention was constructively reduced to practice by the March 31, 1993 filing date of the parent application. Since the application which matured to the Pausch '188 patent was filed, or February 14, 1996, almost one year later, Attorneys for Applicants allege under 37 C.F.R. § 1.608(a) that there is a basis upon which the applicant is entitled to a judgment relative to the Pausch '188 patent.

III. THE REJECTION UNDER 35 U.S.C. §103 (a) SHOULD BE WITHDRAWN

The present invention is concerned with drug screening assays using yeast host cells engineered to express heterologous (*e.g.* mammalian) functional molecular targets. In particular, the invention addresses the problem of how to engineer a non-yeast or heterologous GPCR into a yeast host cell, so that the receptor functions, *i.e.*, transduces a signal, in the yeast cell. To this end, the heterologous receptor must be "functionally coupled" to the yeast host signal transduction system. In other words, the non-yeast GPCR must be able to both receive a signal from its extracellular ligand (or agonist), and forward the signal to downstream effector molecules native to the yeast host. The invention provides a novel solution to the problem of functional coupling by modifying one of the downstream effector molecules in the G protein family -- namely, the Gα protein. In accordance with the invention, a *hybrid Gα protein* is engineered so that it interacts *both* with the non-yeast

GPCR *and* with native yeast downstream effector molecules involved in the signal transduction pathway. These yeast host cells, engineered with "functionally coupled" heterologous GPCRs can be used for drug screening.

The yeast cells defined by the pending claims *require* a *hybrid Gα protein* which productively interacts with a non-yeast or heterologous GPCR. None of the art relied on by the Examiner, whether considered individually or in combination, teach or suggest engineering a yeast cell to produce a *hybrid Gα protein* that productively interacts with a heterologous or non-yeast GPCR expressed by the yeast cell.

Sledziewski's solution to the problem of getting a heterologous receptor to transduce signals in yeast cells is to construct *a hybrid receptor* -- not a hybrid G protein. In Sledziewski, the portion of the receptor that interacts with the extracellular ligand is composed of extracellular domains of a non-yeast or heterologous receptor protein, whereas the portion of the receptor that interacts with downstream effectors of the yeast signal transduction pathway is composed of intracellular domains of a yeast receptor protein. Sledziewski's system uses native yeast G proteins -- not hybrids.

King provides yet a different solution to the problem. In order to get mammalian receptors to transduce signals in yeast cells, King supplies a mammalian Gα protein. Thus, neither Sledziewski nor King engineer a hybrid Gα protein to transduce signals generated by non-yeast receptors in yeast host cells.

The only reference relied on by the Examiner that describes the use of a hybrid Gα protein is Kang. However, Kang's work is not concerned with expression of functionally coupled *heterologous* or *non-yeast* receptors in yeast host cells, *e.g.*, for purposes of drug screening (or any other purpose). Rather, Kang used complementation studies of yeast mutants to analyze how the G protein subunits interact with each other in yeast to transduce signals generated by *native yeast receptors* involved in mating. See Kang at p.2588, col. 2, first full paragraph, "[t]he construction of Scg1 and mammalian Gα hybrids with undertaken to analyze the role of various domains of Gα subunit [citation omitted] in the yeast signal transduction pathway." Kang's data show that the Gα hybrids used in the studies do *not* transduce signals generated by extracellular ligand binding to the yeast receptors, and

Kang concludes that the *Gα hybrids cannot interact with the yeast receptors*. See the summary of the Kang model presented as Figure 5 of Kang which states, "[b]ecause (a heterologous or hybrid Gα protein) cannot interact with the receptor, the pathway cannot be activated, so the cells are sterile." (see Kang, p. 2589, caption to Fig. 5(C)).

Simply put, the prior art does not supply a suggestion or motivation to engineer yeast hosts to produce a hybrid Gα protein that productively interacts with a heterologous or non-yeast receptor. Here, Sledziewski and King, each propose an entirely different solution to the problem. Since each purports to be complete for its intended purpose, one skilled in the art would not have been motivated to depart from their teachings, much less turn to the disparate work of Kang -- especially in view of Kang's negative teaching that the hybrid Gα subunit does not interact with the receptor! See *In re Herschler*, 591 F.2d 693, 200 U.S.P.Q. 711 (C.C.P.A. 1979) (no motivation to substitute ingredients set forth in primary reference where referenced example was already complete for its intended purpose).

Instead, the Examiner contends that one of ordinary skill in the art "would not be dissuaded" from using a hybrid Gα subunit to couple to mammalian receptors in yeast (Office Action, July 3, 2000, p.7, last sentence bridging over to p.8). However, this is not the proper test to support a combination for a finding of obviousness. See *Winner v. Wang*, 202 F.3d 1340, 1349, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000) (affirming district court's finding of non-obviousness, and emphasizing that motivation to combine requires that the prior art teach that it is "desirable" -- not merely feasible -- to make the asserted combination).

CONCLUSIONS

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-captioned patent application. Applicants believe that the foregoing amendments and/or remarks made herein now place the pending claims in condition for allowance. The Examiner is invited to contact the undersigned to arrange an interview with the Attorneys for the Applicants to further discuss the foregoing.

Respectfully submitted,

Date: April 2, 2003

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Enclosures

EXHIBIT A

PENDING CLAIMS
(upon entry of amendment under 37 C.F.R. § 1.111 filed December XX, 2002)
Application No.: 09/286,166 Atty. Docket No.: 11072-009

WHAT IS CLAIMED IS:

43. A transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein.

44. The hybrid Gα protein of claim 43 comprising yeast Gα protein sequences and heterologous Gα protein sequences.

45. The yeast cell of claim 43 further comprising a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, svg1, ste2, and ste3.

46. The yeast cell of claim 45 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

47. The yeast cell of claim 43 wherein the reporter gene is selected from the group consisting of HIS3, URA3, LYS2, CAN1, and Lacz, and the pheromone-responsive promoter is FUS1.

48. The yeast cell of claim 47 further comprising a mutation at a FAR1 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

49. The yeast cell of claim 47 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

50. The yeast cell of claim 43 further comprising a heterologous Gα subunit.

51. The heterologous G protein coupled receptor gene of claims 43 which encodes a receptor selected from the group consisting of a β.2 adrenergic receptor, an α.2- adrenergic receptor, a 5HT-1A receptor, a muscarinic acetylcholine receptor, a growth hormone releasing factor receptor and a somatostatin receptor.

52. The yeast cell of claim 50 further comprising a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, svg1, ste2, and ste3.

53. The yeast cell of claim 52 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

54. The yeast cell of claim 43 and 50 wherein the reporter gene is selected from the group consisting of HIS3, URA3, LYS2, CAN1, and Lacz, and the pheromone-responsive promoter is FUS1.

55. The yeast cell of claim 54 further comprising a mutation at a FAR1 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

56. The yeast cell of claim 54 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

57. The yeast cell of claim 43, 44, 45, or 50 further comprising a heterologous Gα subunit.

58. The heterologous G protein coupled receptor gene of claims 43, 44, 45, or 50 which encodes a receptor selected from the group consisting of a β2 adrenergic receptor, an α2-adrenergic receptor , a 5HT-1A receptor, a muscarinic acetylcholine receptor, a growth hormone releasing factor receptor and a somatostatin receptor.

59. A transformed yeast cell comprising a reporter gene under the control of a pheromone-responsive promoter, a gene encoding a heterologous G protein-coupled receptor, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein.

60. A transformed yeast cell comprising a reporter gene under the control of a pheromone-responsive promoter, a gene encoding a non-yeast G protein-coupled receptor, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein.

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Pages	10 (incl cover sheet)	Date	April 2, 2003

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Application of: Fowlkes et al.	Confirmation No.: 4623
Serial No.: 09/286,166	Group Art Unit: 1646
Filed: April 5, 1999	Examiner: Michael T. Brannock
For: YEAST CELLS ENGINEERED TO PRODUCE PHEROMONE SYSTEM PROTEIN SURROGATES, AND USES THEREFOR	Atty Docket No.: 11072-009 (formerly CPI-012CP4BCN)

Transmitted herewith for filing in connection with the above-identified application is a Supplemental Response and Amendment Under 37 C.F.R. §1.111 and Statement By Laura A. Coruzzi Under 37 C.F.R. § 1.608(a) and accompanying Exhibit A.

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being filed with the United States Patent and Trademark Office by facsimile transmission on April 2, 2003 to facsimile telephone number (703) 746-5238.

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